Expert Report

Mark J. Eisenberg, MD MPH FACC FAHA

Professor of Medicine
Divisions of Cardiology and Clinical Epidemiology
Jewish General Hospital/McGill University
3755 Cote St. Catherine Rd/Rm H-421
Montreal, Quebec Canada H3T 1E2

Tel: (514) 340-8222 x3564
Fax: (514) 340-7564

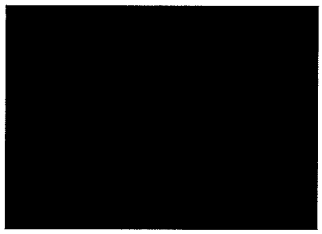

TABLE OF CONTENTS

I. QUALIFICATIONS, BILLING RATE, PRIOR TESTIMONY, AND MATERIALS RELIED ON

1. I am a duly qualified Physician practicing in the Province of Quebec, Canada.

2. I am Board Certified in Internal Medicine with both the Royal College of Physicians and Surgeons of Canada and the American Board of Internal Medicine.

3. My subspecialty is Cardiology. I am Board Certified in Cardiovascular Medicine and Interventional Cardiology by the American Board of Internal Medicine, and I am a Fellow of the American College of Cardiology and a Fellow of the American Heart Association.

4. I am an attending Cardiologist at the Jewish General Hospital in Montreal, and I hold an appointment with McGill University as a tenured Professor of Medicine.

5. I completed my MD at the University of Rochester. I did my Residency Training in Internal Medicine at the Royal Victoria Hospital in Montreal, my Cardiology Fellowship Training at the University of California at San Francisco, and my Interventional Cardiology Fellowship Training at the Cleveland Clinic.

6. I obtained a Master's Degree in Public Health from the Harvard School of Public Health in Boston, Massachusetts.

7. I am the Director of the MD-PhD Program at McGill University, the Director of the Cardiovascular Health Services Research Group at the Jewish General Hospital, and a Principal Investigator at the Centre for Clinical Epidemiology at the Jewish General Hospital.

8. I am an Associate Member of the McGill Department of Epidemiology and Biostatistics, and I was the Director of Clinical Research of the McGill Cardiology Fellowship Program for 18 years.

9. I obtained a Masters of Management in International Health Leadership from McGill University in 2010.

10. I have published over 250 articles in peer-reviewed journals and have performed multiple clinical trials, cohort studies, systematic reviews, and meta-analyses.

11. In 2010, I published a book entitled "The Physician Scientist's Career Guide" (Springer).

12. My research interests include the primary and secondary prevention of cardiovascular disease, health services and outcomes research, technology assessment, smoking cessation, the metabolic syndrome, clinical trials, cohort studies, systematic reviews, and meta-analyses.

13. I have received research funding from the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Canada, and the Quebec Health Research Foundation.

14. In 2013, I was appointed a Fellow of the Canadian Academy of Health Sciences.

15. In my practice, I regularly treat patients with deep vein thromboses (DVTs) and pulmonary emboli. I treat patients with indwelling IVC filters or patients who will be receiving these filters. I commonly prescribe and treat patients with a variety of anticoagulants.

16. I am an interventional cardiologist, and I routinely perform right and left cardiac catheterizations and pulmonary angiograms. I frequently cannulate the inferior vena cava when I perform right heart catheterizations, pulmonary angiograms, and when I insert temporary cardiac pacemakers. The purpose of the pulmonary angiograms is to diagnose pulmonary emboli. The purpose of the right heart catheterizations is to measure and document the pressures on the right side of the heart including the right atrium of the heart which is reflective of the pressures in the inferior vena cava as well.

17. I am cognizant that the IVC is a thin-walled structure that is distensible and that varies in diameter based on volume and pressure conditions. I routinely implant intracoronary stents and insert temporary pacemakers and intraaortic balloon pumps, so I am intimately familiar with a variety of intravascular devices including both temporary and permanent devices. Besides my activities as an interventional cardiologist, I am also a general cardiologist. I perform consultations in the emergency room and elsewhere in the hospital, I round in the Cardiovascular Intensive Care Unit, I perform stress testing, and I have a longitudinal clinic. During these activities, I frequently encounter and treat patients with a history of DVT or pulmonary embolus, and I am frequently called upon to diagnose these conditions.

18. Besides my clinical activities, I am a clinical epidemiologist and I spend approximately 50% of my time doing cardiovascular research. Much of my research involves the design and conduct of clinical trials, the interpretation of data obtained from clinical trials, the critical analysis of safety issues documented in the medical literature in reports of clinical trials, cohort studies, registries, and administrative database studies. I frequently perform systematic reviews and meta-analyses on a variety of topics including medical devices and drugs. My studies typically evaluate the efficacy and safety of medical devices and drugs via a critical review of the published medical literature and, when appropriate, via a statistical pooling of the data.

19. I have been an author on a number of guidelines and consensus statements, and I was a member of the American College of Cardiology Expert Consensus Guidelines Committee for years, so I have experience on how both guidelines and consensus statements are drafted.

20. My current CV is attached as Appendix A.

21. My billing rate is $700 per hour.

22. My prior testimony in the past four years is listed in Appendix B.

II. Conclusions, Standards, and Main Opinions

23. My expert opinions are focused, primarily, on the reasonable expectations physicians have of medical device companies like CR Bard and Bard Peripheral Vascular (hereafter, collectively, "Bard") in their design, testing, manufacturing and marketing of IVC Filters

to allow physicians to properly and completely fulfill their obligations of informed consent as well as decisions by physicians in making appropriate therapeutic decisions on behalf of their patients where an IVC filter may be indicated or considered as a therapeutic option. Moreover, my expert opinions are based on the expectations of what a reasonable patient would want and need to know in the same or similar circumstances for whom an IVC Filter has been prescribed, considered or recommended.

24. The AMA Code of Medical Ethics - CHAPTER 2: OPINIONS ON CONSENT, COMMUNICATION & DECISION MAKING, *2.1.1 Informed Consent* states:

> Informed consent to medical treatment is fundamental in both ethics and law. Patients have the right to receive information and ask questions about recommended treatments so that they can make well-considered decisions about care. Successful communication in the patient-physician relationship fosters trust and supports shared decision making.
>
> The process of informed consent occurs when communication between a patient and physician results in the patient's authorization or agreement to undergo a specific medical intervention. In seeking a patient's informed consent (or the consent of the patient's surrogate if the patient lacks decision-making capacity or declines to participate in making decisions), physicians should:
>
> (a) Assess the patient's ability to understand relevant medical information and the implications of treatment alternatives and to make an independent, voluntary decision.
>
> (b) Present relevant information accurately and sensitively, in keeping with the patient's preferences for receiving medical information. The physician should include information about:
>
> (i) the diagnosis (when known);
>
> (ii) the nature and purpose of recommended interventions;
>
> (iii) the burdens, risks, and expected benefits of all options, including forgoing treatment.

https://www.ama-assn.org/sites/default/files/media-browser/code-of-medical-ethics-chapter-2.pdf.

25. The AMA Code of Medical Ethics' Opinion 8.08 – Informed Consent states:

> The patient's right of self-decision can be effectively exercised only if the patient possesses enough information to enable an informed choice. The patient should make his or her own determination about treatment. The physician's obligation is to present the medical facts accurately to the patient or to the individual responsible for the patient's care and to make recommendations for management in accordance with good medical practice. The physician has an

> ethical obligation to help the patient make choices from among the therapeutic alternatives consistent with good medical practice. Informed consent is a basic policy in both ethics and law that physicians must honor, unless the patient is unconscious or otherwise incapable of consenting and harm from failure to treat is imminent. In special circumstances, it may be appropriate to postpone disclosure of information (see Opinion 8.122, "Withholding Information from Patients").
>
> Physicians should sensitively and respectfully disclose all relevant medical information to patients. The quantity and specificity of this information should be tailored to meet the preferences and needs of individual patients. Physicians need not communicate all information at one time, but should assess the amount of information that patients are capable of receiving at a given time and present the remainder when appropriate.

http://journalofethics.ama-assn.org/2012/07/coct1-1207.html.

26. The ACR–SIR PRACTICE GUIDELINE ON INFORMED CONSENT FOR IMAGE-GUIDED PROCEDURES (Rev. 2016) calls for informed consent for all invasive procedures, and states in pertinent part:

> Prudent and ethical medical practice requires close communication between the patient and the physician. If the patient is unable to provide consent, the patient's legal representative or, in the case of a minor, the patient's parent(s) or legal guardian, represents the patient in the consent process. The patient or representative and, when appropriate, the patient's family must have every opportunity to understand the treatment or procedure the patient is to receive and its reasonable risks, benefits, and alternatives; to have all questions answered; and to fully consent to the treatment and procedure.
>
> I. INTRODUCTION
>
> This guideline was revised collaboratively by the American College of Radiology (ACR) and the Society of Interventional Radiology (SIR). Prudent and ethical medical practice requires close communication between the patient and the physician. The patient, or if the patient is unable to provide consent, the patient's legal representative and, when appropriate, the family, must have every opportunity to understand the treatment or procedure the patient is to receive and its reasonable alternatives, to have all questions answered, and to fully consent to the treatment and procedure. The degree of disclosure required for a valid consent varies from state to state, but there are two generally recognized legal standards. The first is measured by what a reasonable physician in his or her professional judgment believes is appropriate to disclose to the patients. The degree of disclosure depends on perceptions of the physician in each case. The second legal standard is based on what a reasonable patient would want to know in the same or similar circumstances.

> The legal trend is towards the "reasonable patient" standard, which usually requires greater and more detailed disclosure of information.
>
> ...
>
> B. Protocol for Informed Consent for Elective Procedures
>
> 1. Before the proposed procedure is performed, the following will be explained to the patient or, if the patient is unable to provide consent, to the patient's legal representative:
>
> a. The purpose and nature of the procedure or treatment.
>
> b. The method by which the procedure or treatment will be performed.
>
> c. The risks, complications, and expected benefits or effects of such procedure or treatment.
>
> d. The risk of not accepting the procedure or treatment.
>
> e. Any reasonable alternatives to the procedure or treatment and their most likely risks and benefits.
>
> f. The right to refuse the procedure or treatment.
>
> https://www.acr.org/~/media/1A03224CA4894854800C516012B6DB5A.pdf.

27. The totality of the evidence indicates that there are much higher complication rates associated with the Recovery, G2,[1] and Eclipse IVC filters versus the Simon Nitinol Filter (SNF). These higher complication rates indicate that neither the Recovery nor the G2 are substantially equivalent to their predicate devices. Similarly, the evidence indicates that both Meridian and Denali had higher rates of fracture than SNF, and while there is apparently limited information on other adverse events associated with these devices, fracture can lead to tilt, migration, and perforation.

28. Former head of Regulatory Sciences for C.R. Bard, Chris Ganser, testified at deposition on October 11, 2016, that he would want his "doctor to have the safety profile, the risk evidence that exists as to each device so that doctor could make (an informed) choice" and that "It's true I want the doctors to have as much information as possible to make an informed decision how to use the product" and that "all patients deserve that right for their doctors to be fully informed of all of the potential information about risks and benefits so that the doctors can make an educated choice for the patient." (Ganser deposition, 10/11/16, 208:2-22; see also, 237:21 – 238:20). I agree with Mr. Ganser and a reasonable physician would expect no less of his company in their marketing of IVC Filters. I also agree with former Vice President of Quality Assurance of C.R. Bard, Douglas Uelman, that the more

[1] For purposes of this analysis, I consider the G2 and G2x filters to be the same because the changes made to the G2 to develop the G2x filter did not change the safety profile of the filters. See section regarding Development and Release of Filters.

information companies like Bard share with doctors about their IVC filters, the better. (Uelman deposition, 10/4/13, pg. 340:17-341:6).

29. I also agree with Mr. Ganser that if there exists reasonable evidence that their IVC filters are not performing as represented, intended or expected, the company should consider recalling the device and stop selling it. (Ganser deposition, 10/11/16, 97:24-98:3).

30. There were multiple early safety signals evident with the Recovery G2, Eclipse, Meridian, and Denali filters. These signals came from adverse event reports/sales data, from reports in the medical literature, and from Bard's own in vitro testing [redacted] See Dr. Rebecca Betensky expert report and references).

31. Despite these three lines of evidence demonstrating high rates of complications with the filters, Bard did not address these issues in a way that accurately and timely disclosed or explained the risk to physicians. Bard also did not undertake measures that would have further explored and clarified the safety issues with these filters as compared with the SNF. [redacted]

32. Instead of exercising the kind of transparency physicians and patients expect from a medical device company like Bard, Bard continued to represent these devices as new and improved compared to predicate and competitor devices. For example, one of Bard's marketing messages was that its devices "take strength and stability to a new level," and [redacted]

33. Because Bard should not have expected later generation devices to address/mitigate all of the problems occurring in the Recovery and G2 filters, it was misleading for Bard to represent in marketing materials and to physicians that the newly launched devices were substantial improvements over previous ones. It was also misleading and detrimental to patient health, safety and informed consent to continue to sell the earlier devices after the newer ones had been cleared for marketing.

34. As a physician with patients who are candidates for IVC filters, or have them implanted, I would expect that the adverse events seen in the Asch retrievability study and the Everest study should have prompted prospective large well-conducted safety studies. Such studies would have clearly defined the severity and extent and timing of complications associated with IVC filters. It was clear from the adverse event reports/sales data as early as 2004 there were safety issues. Data from the Asch study and from in vitro testing were available even earlier.

35. It was clear that there was a need for large prospective studies with systematic clinical and imaging follow up with long term outcomes. It would not have been difficult or onerous to

do such a study. "If you don't want to know the answer, then don't look." This is essentially what happened.

36. Instead, Bard effectively allowed patients to be experimental subjects. Patients who had these filters implanted in their blood vessels were not informed of the design problems and complication risks. (Ganser deposition, 10/11/16, pgs. 65:8-66:24; 85:21–86:23; 215:23-216:7; 237:3-238:20).

37. As a physician with patients who are candidates for IVC filters, or have them implanted, I would expect that [redacted] As a physician with patients who are candidates for IVC filters, or have them implanted, I would expect that neither the Recovery nor the G2 should have been marketed [redacted]

38. Despite internally monitoring adverse event reports/sales data regarding complication rates, Bard did not make this information available to clinicians or their patients.

39. When it became evident that clinicians were switching to other brands of IVC filters because of concerns about complications, [redacted] to [redacted]

40. As a clinician, with patients who are candidates for IVC filters, or have them implanted, and as a clinical epidemiologist with expertise in clinical trial design and interpretation of the results of clinical studies, I do not view the high rates of complications with Recovery G2, Eclipse, Meridian, and Denali compared to SNF as "substantial equivalence." Had I been made aware of these data, I would not have used Bard filters, and would have advised my colleagues to avoid exposing their patients to these devices. The low tolerance for filter fracture, migration, tilt and perforation complications is not mine alone. I believe this standard is shared widely among experts in the field.

41. Future complications are very likely to become evident in patients with implanted Recovery G2, Eclipse, Meridian, and Denali filters. Since there has only been intermittent and non-systematic follow up of patients, it is likely that many more complications will be found in the future. Patients could potentially have these filters in for decades. Long term monitoring and systematic imaging are required in these patients.

42. The standards that underlie my opinions in this report for monitoring for safety signals, following up on those signals, and disclosing important safety concerns to doctors, form the foundation of our medical system, are essential for informed consent and patient safety, and constitute generally accepted standards for pharmacovigilance. See FDA, Guidance for Industry, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (March 2005). *See also* World Health Organization The IMPORTANCE of

PHARMACOVIGILANCE Safety Monitoring of medicinal products (2002). http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf?ua=1.

43. These standards are generally accepted, not controversial, and are recognized by Bard's president, Steven S. Williamson, as applicable to Bard. *See* Williamson Deposition, 9/7/16, and the deposition of a Bard physician consultant, Dr. Anthony Venbrux, taken on1/26/17, at pgs. 91:18-92:9.

44. Mr. Williamson agreed Bard had an obligation to make safe medical devices ("as safe as it can reasonably make it before it sells the product,") and that Bard should "take all reasonable steps to ensure that a device is safe and as free of dangers as it can be before putting the device on the market (p. 110).

45. Mr. Williamson agreed that Bard should perform "all reasonable tests to ensure the safety of the device," and that the device should be "reasonably tested" and that Bard should perform "reasonable clinical work …to ensure the safety of the product." (pp. 110-113). He agreed Bard should perform "clinical trials [that are] reasonably designed to discover potential safety problems." (p. 114). He agreed that Bard should look for safety signals, and if there are signals "It would be a signal to me to make sure that I did a further investigation to look deeper on it." (p. 164). He agreed that important safety information must be disclosed to doctors. ("we provide the physician, who is our customer, the information, and we would provide them information on things that a reasonable doctor would want to know…" (p. 344). This includes informing doctors if later generation devices are safer than other devices. (p. 349-50). This also includes informing doctors about increased complication risks, fracture risks, migration risks, and tilt risks because "migration stability [and] lack of tilt is important to doctors." (p. 351-352).

46. I agree with Mr. Williamson regarding the importance of meeting these internal standards to assure patient safety. As discussed in this report, Bard did not adhere to its own internal standards, as recognized by its president, Steven S. Williamson. Bard also has not met the standards set forth by FDA in its Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.

47. [redacted]

48.

defined as 1 in 100 uses (or more often), which translates to a rate of 1%. (RA-STD-002, BPV-17-01-00024667, pg. 13).

49. [redacted]

50. My opinions about what a reasonable physician would have relied on and considered to be important are supported by the guidance documents published by the FDA and various radiological societies. In the years since the complications with retrievable filters have come to light, these documents note that the benefits of retrievable devices have not been demonstrated and, if used, should be removed as soon as possible. (2010 and 2014 FDA Safety Alerts, Health Canada 2016 Safety Alert, ACR-SIR-SPR Practice Parameters, 2016 and 2017 revisions).

III. Methods

51. The methodology that I followed in this case is the same as my methodology in my medical research and in my clinical practice. Specifically, in forming my opinions in this case I endeavoured to consider the totality of the evidence based on my review of published medical literature, internal Bard documents,[2] depositions, expert reports, my clinical experience, and my experience in teaching and in my academic medical research and writing. I did my own research of the published medical literature and also reviewed medical literature provided to me by plaintiffs' counsel. Specifically, I used the same standards for evaluating and interpreting medical and scientific evidence that I use in my work outside the courtroom.

52. To assess the medical and scientific evidence, I used the same standards that I use in my clinical practice and in my other professional work. I considered the methods, strengths and limitations of each study as I would do in my work outside of the courtroom. I base my opinions based on my assessment of the weight of the evidence, using the same standards and criteria that I use in my professional work. To consider the appropriate weight, I consider a range of factors: Has or can the study been replicated? Does the study address the outcome of interest? Has the study been conducted on a relevant population for the current issues? Is there a statistical analysis, with a reported error rate? Do the results

[2] I obtained internal Bard documents from plaintiffs' counsel. I understand that there are several million documents produced by Bard in this litigation. In my meetings and conversations with counsel regarding the topics in this report, I informed them of my interest in certain categories of documents bearing on those issues.

make biological sense? What is the size of the study population, and is the study adequately powered to draw conclusions regarding safety or efficacy? What type of study was it? Did the study assess safety issues in a manner that conforms with medical standards? This is a list of examples, and is not intended to be comprehensive.

53. I also consider whether the evidence is consistent with other evidence.

54. I was asked by the plaintiff's legal counsel to provide opinions to assist the jury in several areas. I was asked to review publicly available published materials and Bard internal documents obtained in discovery to offer opinions about whether and when there were safety concerns which could trigger obligations to inform physicians, and patients about the nature of the safety concerns. I also was asked to review the clinical trials (including Asch and "Everest") to determine and help explain the purpose and findings of these studies and whether they met the criteria to qualify as safety studies. I also was asked to assess whether these devices were as safe as their predicate devices based on the available evidence. I also was asked to explain whether the "Grassi" article provides an industry standard for acceptable complication rates, and to assess the defense arguments for use of the MAUDE data in connection with this paper.

55. My opinions about what Bard should have done or information it should have communicated to physicians are with respect to physician expectations, and based on my experience as a physician and from conferences and other venues where physicians express their opinions. As noted above, my opinions are based on established and accepted objective standards referenced above, including Bard's internal standards.

IV. Data Considered/Relied On And Opinions

A. DEVELOPMENT AND RELEASE OF THE RECOVERY, G2, ECLIPSE, MERIDIAN, AND DENALI FILTERS

56. In order to offer these opinions, I undertook to develop a deeper understanding of the history of the Bard IVC filters and the information known to Bard based on their internal documents and deposition testimony. This information provides the necessary context and foundation for my opinions, which depend on the particular facts available to and known to Bard, and form part of the basis for my opinions.

57. Permanent IVC filters have been available for several decades. The Greenfield filter was the first permanent IVC filter that could be implanted via a percutaneous procedure. (Greenfield LJ, Historical Reminiscence: Origin of the Greenfield Filter, 76 Am Surg 1319, 1319-20 (2010)). The Simon Nitinol Filter (SNF) was a permanent IVC filter that received FDA clearance in 1990 (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K894703) and was the first Nitinol IVC filter on the market. There is an FDA document reporting on the safety of the SNF (US FDA Clinical Data Summary of the Simon Nitinol Filter). [redacted]

[redacted]

58. [redacted]

59. To implement its strategy to market a retrievable IVC filter, Bard acquired the Recovery IVC filter line from NMT (BPVE-01-00242737).[3] Bard had been marketing the SNF for approximately a decade and was intimately involved with the design and testing of the Recovery even before the purchase went through.

60. Besides Bard, other companies were simultaneously developing retrievable filters including the Gunther Tulip by Cook (FDA clearance: retrievable indication 2003) and the Optease by Cordis (FDA clearance: with retrievable indication 2004).

61. In order to obtain FDA clearance for the Recovery filter, Bard submitted an application to the FDA using the 510(k) pathway to gain clearance (11-27-2002 510(k) submission). BPV–Trial-Exhibit–0293. In their application, Bard indicated that the SNF and Titanium Greenfield K90-1659 were the predicate devices for the Recovery filter and that the Recovery filter was substantially equivalent to the SNF. Using the 510(k) process, Bard was able to obtain expedited clearance for the Recovery filter as a permanent IVC filter.

62. At the time Bard purchased the Recovery filter from NMT, the 510(k) for the Recovery filter had been rejected twice by the FDA on the basis that NMT could not demonstrate it

[3] Bard began distributing the SNF in 1992 in the US. NMT modified this design (the SNF) (BPVE-01-00242737), and called it the Recovery Filter. NMT filed a special 510(k) for clearance of the Recovery in 1999, which was initially rejected by the FDA. (BPV-17-01-00051623).

was the substantial equivalent to the SNF. In the second rejection, the FDA specifically stated that NMT must prove that the Recovery filter had similar performance characteristics to the SNF as far as migration, fracture, and perforation. Vierling Dep. Exhibit 225; Vierling Dep. pg. 12-22; BPV- 17-01-00051625–26). At no time did Bard ever show that the Recovery had similar performance characteristics to the SNF.

63. Bard received a letter from the FDA dated October 25, 2002 stating that FDA had reviewed the 510(k) application and had determined that Recovery filter is substantially equivalent to the legally marketed predicate device (BPV-TRIAL-EXHIBIT-1245). Thus, the FDA allowed Bard to market the device. However, the letter further says that the following statement must appear in the Precautions section of the device's labeling and promotional materials: "The safety and effectiveness of the Recovery Filter for use as a retrievable or temporary filter have not been established."

64. Following a small study performed by Dr. Murray Asch (Asch MR. Initial experience in humans with a new retrievable inferior vena cava filter. Radiology. 2002; 225:835-844), Bard was able to obtain FDA clearance to market the Recovery filter. (BPV-17-01-00057981). Bard marketed the Recovery as a permanent filter in 2002 and as a retrievable filter in 2003 (FDA clearance: permanent indication 2002; retrievable ("optional") indication 2003).

65. [redacted]

66. [redacted]

67. [redacted]

[redacted]

68. Similar to the process used to obtain FDA clearance for the Recovery filter, Bard used the 510(k) pathway in which Bard indicated to the FDA that the Recovery filter was the predicate device for the G2 filter and that the G2 filter was substantially equivalent to the Recovery filter – again, and similar to the Recovery – without large safety and efficacy studies. After obtaining clearance for a permanent indication for the G2 filter in 2005, Bard initiated a small retrievability study known as the Everest trial (Binkert CA, Drooz AT, Caridi JG et al: Technical success and safety of retrieval of the G2 filter in a prospective, multicenter study. J Vasc Interv Radiol 2009; 20:1449-1453; Bard Recovery G2 Filter Study - EVEREST Final Study Report (BPVE-502d-00000013 – 103). Bard learned of the Everest results two years prior to publication of the Everest trial. Following this study, Bard obtained clearance for a retrievable indication from the FDA for the G2 filter in 2008. (BPV-17-01-00123590).

69. [redacted]

70. Bard made various incremental changes to the G2 filter to create the G2x filter, cleared through the Special 510(k) process. (http://www.fda.gov/cdrh/510k/K080668.pdf, last accessed on January 27, 2017). The only changes were the addition of a snare tip and "minor dimensional modifications" to the delivery system.

71. [redacted] The Eclipse was cleared in January, 2010 (http://www.accessdata.fda.gov/cdrh_docs/pdf9/K093659.pdf (last visited 2/3/17); BPVE-01-00761124), which was then followed by the Meridian filter (which added caudal anchors, and was cleared in August, 2010 BPVEFILTER-0-00432649), and most recently by the Denali filter, cleared in May, 2013, and incorporating cranial anchors, caudal anchors, penetration limiters, and electropolishing. (BPVEFILTER-01-004780).

72. All of these design changes incorporated into the Eclipse, Meridian and Denali were [redacted]

[redacted]

B. ASCH RETRIEVABILITY STUDY FOR THE RECOVERY FILTER

73. Dr. Murray Asch was commissioned by Bard to do the first retrievability study with the Recovery filter (Asch MR. Initial experience in humans with a new retrievable inferior vena cava filter. Radiology. 2002; 225:835-844). Dr. Asch is an interventional radiologist and a fellow of the Society of Interventional Radiologists (SIR). Dr. Asch identified 3 complications in the first 33 patients that he studied – one case of filter migration and two filter fractures in a second patient. (BPVE-01-00054540; BPV-17-01-00052603). He had not previously seen a fracture in other patients or devices (Asch Declaration/Affidavit, par. 15). He reported the fracture to Rob Carr at Bard. This is a "safety signal": The occurrence of these complications in a 33 patient study raises the concern that when the device is released for marketing to thousands of people, the complication rate will be unacceptably large.

74. Dr. Asch testified that his study was a pilot study for the Recovery filter and that Bard advised him that it would subsequently do a large safety study. (Deposition of Dr. Murray Asch on May 2, 2016 pg. 43:10-21). When this was never done, Dr. Asch testified that he had been misled by the company. (Deposition of Dr. Murray Asch on May 2, 2016 pg. 165:2-10). In my opinion, the Asch study was not a safety/efficacy study. It was a pilot study which employed a small sample size which was only designed to examine the retrievability of the Recovery IVC filter. I agree with Dr. Asch that this study does not offer reliable evidence of safety or efficacy or of substantial equivalence. Based on my calculations, the study was not powered to examine either the safety or efficacy of the Recovery filter. I agree with Dr. Asch's assessment.

75. Without Dr. Asch's knowledge, Bard used the results of his study for regulatory purposes to obtain clearance for a retrievability indication for the Recovery filter from the FDA. (BPV- TRIAL-EXHIBIT-0293, 0029 - 0033). Following the commercial release of the Recovery filter, Bard and Dr. Asch independently became aware of reports of adverse complications associated with the filter.

76. Dr. Asch asked Bard for help in tracking the patients in whom he had placed Recovery filters but Bard refused. Asch Dep. p. 208- 209. I agree with Dr. Asch that "There is an unacceptably and dangerously high rate of complications which lead to injury and death that have been identified with the Recovery filter that is not present in other filters that I have used in my practice." Asch Declaration, par. 27.

77. He further stated: "Since 2002, fracture of the Bard Recovery and other Bard filters has been reported extensively in the medical literature revealing data showing that the Recovery and G2 filters present an unreasonable and unsafe risk of harm to patients in whom the devices are implanted." Asch Declaration., par. 29. Because of the high complication rates associated with the Recovery filter, he recommended a monitoring and surveillance program for patients with these filters. I agree with Dr. Asch's assessments.

C. POST-MARKET SURVEILLANCE – ADVERSE EVENTS REPORTS

78. Physicians (including myself) expect medical device manufacturers to monitor the safety of their devices through appropriate testing, including bench testing, animal testing, adequately powered studies, and post-market surveillance. Post-market surveillance includes monitoring of spontaneous adverse event reports and comparisons with other products—both predicate and competitor devices. Physicians, like me, who work with patients who have IVC filters specifically expect IVC manufacturers, including Bard, to conduct these analyses and convey any notable results to physicians and patients.

79. The FDA maintains a database (known as MAUDE) to facilitate this process. Adverse event data is valuable for identifying signals of safety problems and based on analyses of the data, additional, valuable information, including comparative information) can be obtained. Physicians, including myself, expect companies to also use internal data to appropriately monitor the safety of their devices. The analyses of this data is especially crucial when there exists no controlled clinical trial that assesses the relative risks of these devices. [redacted]

80. This description of the MAUDE database is taken directly from the FDA website (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm): "MAUDE - Manufacturer and User Facility Device Experience. Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. The MAUDE database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use."

81. The MAUDE database is a sentinel identification system. The objective of this system is to identify adverse safety signals with medical devices. If these signals are identified, companies have the responsibility, as Bard itself, by its president recognizes, and also based, in part on physician expectation and medical ethics to follow up with properly designed and adequately powered studies. In my opinion, if an adverse safety signal is identified and a company does not adequately follow-up, the company is responsible for the consequences to the patients who were implanted with their products. The reason for the standard in medicine to identify safety signals and follow-up appropriately is because this is an accepted method for gathering information which is essential for protecting public health and patient safety.

82. [redacted]

[redacted]

83. The reports of elevated rates of adverse events came from two principal sources: 1) analyses of adverse event reports and sales data and 2) reports in the medical literature. These sources were complemented by in vitro (bench) testing that was done internally by Bard.

84. [redacted]

85. The above documents demonstrate that Bard was closely tracking adverse event data over the course of years regarding adverse events with both the Recovery and G2 filters. [redacted]

[redacted]

86. [redacted]

87. [redacted]

88. Applying Bard's RA-STD-002 standard (described above) to Bard's IVC filters demonstrates that Bard should have determined that the filters performed unacceptably and should have been corrected.

89. [redacted]

[redacted]

90. To evaluate whether Bard's filters met its internal standard, I reviewed the rates of reported device failures based on Bard's internal tracking and sales data. This provides a minimum frequency because spontaneous adverse event reports do not provide "actual" frequency. To calculate a "statistically derived frequency" of occurrence, one would have to determine the underreporting rate and multiply by that amount. At least one study has attempted to derive the underreporting rate for medical devices. FDA Center for Devices and Radiologic Health, "Ensuring the Safety of Marketed Medical Devices CDRH's Medical Device Postmarket Safety Program" (2006), available at http://www.fda.gov/ohrms/dockets/dockets/06n0292/06n-0292-bkg0001-08-Tab-07-vol2.pdf (last visited January 20, 2017). Based on this analysis, the underreporting rate for medical devices, generally, is approximately 86%. *Id.*, p. 56. Meaning that a reporting rate of .014% would result in a statistically derived frequency of 0.1%, putting it in the "unacceptable" range and requiring a correction. Nicholson, et al. put the underreporting rate at 90%. (Nicholson W, Nicholson J, Toerico P, et al. Prevalence of fracture and fragment embolization of Bard retrievable vena cava filters and clinical implications including cardiac perforation and tamponade. Arch Intern Med 2010 170:1827-31). While David Ciavarella agreed that to 1 to 5% of adverse events are reported (Ciavarella Deposition, 11/12/13, p. 128:10-20). See also (Ganser Deposition, 10/11/16, p. 234:13-234:24, 235:10-236:4). Even without correcting for underreporting, [redacted]

[redacted]

D. HEALTH HAZARD EVALUATIONS AND OBSERVATIONS AND RECOMMENDATIONS BY CONSULTANT DR. JOHN LEHMANN

91. According to David Ciavarella, the Staff Vice President, Corporate Clinical Affairs at Bard, the purpose of a Health Hazard Evaluation (HHE) is to formally analyze and document the potential ramifications of a hazard to a patient (Deposition of David Ciavarella, MD; November 12, 2013, p. 46).

92. [redacted]

[redacted]

93. [redacted]

94. [redacted]

95. [redacted]

96. [redacted]

97. [redacted]

[redacted]

98. [redacted]

99. [redacted]

100. [redacted]

101. [redacted]

102. [redacted]

[redacted]

103. [redacted]

104. [redacted]

105. [redacted]

[redacted]

106. [redacted]

E. BETENSKY ANALYSES – ADVERSE EVENTS

107. The elevated reporting rates of adverse events identified by Bard's internal consultant were recently confirmed by an expert consultant – Dr. Rebecca Betensky - a Professor of Biostatistics at the Harvard School of Public Health (Betensky Report 2017).

108. Dr. Betensky's analyses confirm what Bard was seeing with their own analyses of the data – much higher complication rates associated with the Recovery filter versus the Simon Nitinol Filter. Dr. Betensky extended Bard's analysis to subsequent time periods for the Recovery filter, and to evaluate what Bard could have seen with respect to reporting rates for the G2, Eclipse, Meridian, and Denali filters compared to the SNF. As Bard had done internally, Dr. Betensky used adverse event reports for the numerator and Bard's own sales data for the denominator in order to calculate reporting rates for each device. She then divided the rates for the newer device by the rates for the predicate device in order to generate a reporting risk ratio, which is an estimate of the increased risk associated with the Bard devices compared with the predicate device.

109. Dr. Betensky's analyses show highly statistically significant differences (and higher complication reporting rates) for the Recovery, G2, Eclipse, Meridian, and Denali versus SNF. These analyses confirm the high rates of adverse events that Bard was internally identifying with their analyses of its adverse event and sales data shortly after it began selling each filter. Dr. Betensky also identified some errors in Bard's data that it used during its analyses. These errors were likely transcription errors but, when corrected, actually magnified the size of the complication rate differences.

110. Dr. Betensky found that as early as the second quarter of 2003, the Recovery filter was associated with a statistically significant higher reporting rate of migration versus SNF. (Betensky analysis) By the third quarter of 2004, the Recovery filter was associated with statistically significant higher reporting rates of filter embolization deaths, migration, caval perforation, and fracture. Dr. Betensky also found that the G2 and G2x were associated with high reporting rates of adverse events. Finally, her analysis of the Bard data revealed that the Eclipse, Meridian, and Denali were associated with statistically significant higher reporting rates of fractures shortly after the launch of each filter (one year or less of sales).

111. Dr. Betensky acknowledged several potential limitations of her analyses. First, under-reporting of events is a potential limitation. However, Dr. Betensky makes the point, which I agree with and which is well-accepted, that although under-reporting is likely with spontaneous adverse event reports, this in and of itself will not lead to bias unless there is differential under-reporting between devices. Second, she could not calculate person-time exposure. These data are not available from the adverse event reports and Bard internal sales data that she used. The longer a patient has a device implanted, the more at risk they are for complications. However, Dr. Betensky makes the point that the SNF implantation time is much longer than that of the retrievable filters but that reporting rates are much higher with the latter. This finding goes against the idea that exposure time would change her observations. Rather, any adjustment for exposure time would likely result in a higher relative rate of adverse events for Recovery, G2, Eclipse, Meridian, and Denali. Third, Dr. Betensky notes that temporal effects in reporting (Weber effect) can occur. Thus, more adverse events may be reported just after the release of a drug or device and this may wane over time. However, she discounts this possibility because the high reporting rates with the retrievable filters were higher than those of other retrievable filters and they did not wane over time. Fourth, she notes that reports generated by publicity ("notoriety effect" or "stimulated reporting") can occur. Thus, following an FDA warning or following media reports, these events may stimulate an upsurge in reporting of adverse events. However, she was not aware of any effect of this nature with the retrievable filters, and nor am I aware of any such effect. Lastly, confounding or "channeling bias" can occur. Thus, if there is a risk factor that is associated with the use of a particular device and a particular adverse event, bias could occur. Again, however, she noted that there is little evidence that patients who are at higher risk for complications would have been preferentially implanted with the retrievable filters so that this potential limitation does not appear to have any basis in fact. In my opinion, such an effect would be unlikely to be of sufficient magnitude and specificity to affect the results seen.

112. Thus, Dr. Betensky's analysis of the adverse event/sales data strongly confirmed what Bard was seeing internally as early as 2004 -- that there were statistically significant, elevated adverse event rates associated with the Recovery, G2, Eclipse, Meridian, and Denali filters compared with the SNF.

F. IN-VITRO DATA – ADVERSE EVENTS

113. [redacted]

[redacted]

114. [redacted]

115. [redacted]

116. [redacted]

117. [redacted]

G. LATER GENERATION DEVICES – ECLIPSE, MERIDIAN, AND DENALI

118. The safety signals and complications known to Bard with respect to the Recovery and G2 devices led to design changes leading to the Eclipse, Meridian and Denali devices. To the extent that the design changes in these later generation devices did not adequately address the known problems with the Recovery and G2, the later generation devices would be expected to have the same problems. As explained by Dr. McMeeking (McMeeking Report, 1/27/2017), the changes from the G2 to the Eclipse, and from the Eclipse to Meridian were not properly tested or validated, and should not have been expected to substantially reduce fractures, or have any effect on the other problems occurring in the G2. Dr. McMeeking's report is consistent with the conclusion that these later devices share the same problems as the G2 and Recovery. To the extent Bard failed to disclose this, or claimed that the later devices were substantially safer, this was misleading to doctors using filters and interfered with principles of informed consent.

119. To the extent that the later generation devices were substantially the same design as the earlier devices, the safety signals from the earlier devices would apply to these later generation devices. Physicians using these devices or considering them for their patients, including myself, would expect Bard to undertake adequate bench testing and adequately powered safety studies to assure that the new filters corrected the problems in the earlier devices and did not raise new questions about safety. These studies are necessary for patient safety.

120. Mr. Modra testified that the occurrence rating is an important part of Bard's risk assessment. (Chad Modra Deposition, 1/27/17, p. 120-121). He also testified that, prior to launch, it was important for Bard to accurately determine the occurrence rates for failures such as migrations, penetrations, perforations and fractures. (Chad Modra Deposition, 1/27/17, p. 121).

121. I understand that Dr. Betensky will testify that Bard's internal risk assessment estimated that the G2, G2Express, Eclipse, Meridian, and Denali filters were more likely to have reports of migrations, penetrations, perforations and fractures than the SNF, which is the initial predicate for all of these devices.

122. I understand that Dr. Betensky will testify that Bard estimated that the failure rates for migrations, penetrations, perforations, and fractures in many categories would overall be higher for the Recovery, G2, G2Express, Eclipse, Meridian and Denali than the SNF. Mr. Modra was specifically questioned as to the comparative estimated failure rates of the G2Express at launch, and the SNF. [redacted]

123. [redacted]

[redacted]

124. Physicians would also expect Bard to disclose to them the problematic history of the earlier devices. I have seen no evidence that those disclosures have been made. These disclosures are necessary for patient safety and to allow for informed consent.

125. [redacted]

126. [redacted]

127. [redacted]

128. [redacted]

129. [redacted]

[redacted]

130. [redacted]

H. MEDICAL LITERATURE – ADVERSE EVENTS

i) Recovery Filter Studies

131. Multiple studies in the medical literature examined the retrievability of the Recovery filter. Although these studies were not powered to examine efficacy or safety, these studies documented a high incidence of complications associated with the Recovery Filter.

132. In 2002, Asch published a series of 32 Canadian patients who received the Recovery filter (Asch MR. Initial experience in humans with a new retrievable inferior vena cava filter. Radiology. 2002; 225:835-844). Importantly, one patient was noted to have a 4 cm migration of their filter. In addition, the 33rd patient, who was not included in the original report, suffered two filter fractures. This later report indicated that out of 35 patients, there was at least one instance of IVC perforation (3.7%), and one instance of tilt after insertion (and a possible additional "penetration") (3.7%), for a combined complication rate of 14.8% (BPV-17-01-00057981).

133. A 3.7% rate of having a filter migration and/or fracture, and a 14.8% complication rate is high for these type of complications, and would have impacted physician treatment decisions had it been known to them. This observation alone should have prompted larger safety studies before the filter was released commercially.

134. In 2005, Grande et al. published a retrospective analysis of 106 patients who received Recovery filters. (Grande, et al., Experience with the Recovery Filter as a Retrievable Inferior Vena Cava Filter, J Vasc Interv Radiol 2005; 16:1189–1193). A retrieval attempt was made in only 15 cases (14%), out of 14 retrieval attempts after successful placement, there was one failed retrieval (7.1%). The authors reported symptomatic PE after filter placement in 3 patients (2.8%), and one case of possible IVC thrombus. The authors concluded: "Long-term studies of the safety and efficacy of the Gunther Tulip, Optease, and Recovery filters when used as permanent filters are needed." They also concluded that: "Although all the filters were placed with the intention of being removed, a large percentage of filters were not retrieved."

135. The Grande et al. article is representative of many medical reports published in this area. A large number of these reports state that even though retrievable filters were implanted in patients, only a small minority of these filters were ever retrieved. This finding calls into question the use of retrievable filters in the first place. In addition, the Grande et al. article as well as others indicate that there is a not insubstantial rate of inability to retrieve "retrievable" filters (7.1% in the Grande et al. article), and that a not insubstantial number of patients implanted with these filters still develop pulmonary emboli and further have the known IVC filter – related complication of IVC thrombus.

136. In 2006, Kalva et al. published a retrospective analysis of 96 patients who received the Recovery filter at the Massachusetts General Hospital (Kalva SP, Athanasoulis CA, Fan CM et al. Recovery vena cava filter: experience in 96 patients. Cardiovasc Intervent Radiol 2006; 29:559-64). Of the 96 patients, only 11 had a retrieval attempt, 9 of which were successful. One of the 9 had an IVC thrombus and 1 had an IVC tear associated with retrieval. Of the 40 patients who had an abdominal CT at a mean of 80 days, there was a high rate of adverse events: penetration of the IVC – 11 patients (3 of whom had filter fracture); migration of broken arm into the pancreas – 1; and asymmetric deployment of the filter legs -12. The authors concluded that the Recovery filter "...is associated with structure weakness, a high incidence of IVC wall penetration, and asymmetric deployment of the filter legs."

137. The adverse event rates reported in this study are extremely high and would have dissuaded most physicians from using this device if it had still been on the market. As mentioned above, the Recovery filter had been withdrawn from the market in September 2005, before the Kalva study was published. The high rate of complications in the Kalva study is consistent with the high reporting risk ratio data developed by Bard in 2004, which were not disclosed to doctors or patients. Moreover, in the interest of patient safety, and consistent with its own standards of following up with necessary studies when faced with safety signals, Bard should have conducted a multi-center study expanding the Kalva study while the Recovery filter was on the market to determine whether problems such as these were occurring on a wide scale basis and to quantify the risk, and develop a better understanding of the nature of the problem.

138. In 2007, Karmy-Jones et al. published a retrospective review of 599 filters placed at 21 participating centers, with 6-month follow-up. (Karmy-Jones, et al., Patterns and Outcomes of Retrievable Vena Cava Filters in Trauma Patients: An AAST Multicenter Study, J Trauma 2007:62:17–25). A total of 224 of the filters were Recovery, of which 50 (22%) retrieval attempts were made, and 14% were unsuccessful. Migration was detected in 1.3% of Recovery filters, and symptomatic caval occlusion in 1%. The authors noted that "recently the Recovery has been withdrawn and re-designed specifically because of concerns regarding its durability as a permanent filter." They also noted that "the Bard-Recovery has been recently "modified" because of concerns about strut fracture and migration."

139. In 2009, Hull and Robertson published the results of a retrospective cohort of patients who received the Recovery filter (Hull JE, Robertson SW. Bard Recovery filter: evaluation and management of vena cava limb perforation, fracture, and migration. J Vasc Interv Radiol

2009; 20:52-60). At long term follow-up (mean 899 days), all 14 patients had filter arm perforations; 36% had leg perforations; and 21% had fractures associated with migration. The authors concluded that Recovery filter limb perforation increases over time and is associated with a 21% incidence of filter arm fracture and migration. The authors recommended follow up imaging for patients receiving these filters.

140. These rates are very high and would preclude the use of this device.

141. In 2010, Nazzal et al. published a retrospective review of all filters placed at their institution. (Nazzal, et al., Complications Related to Inferior Vena Cava Filters: A Single-Center Experience, Annals of Vascular Surgery, 24:4, 480-486, 2010). Of 400 filters placed, 34 were Recovery filters and 5 were SNF. The authors reported that 2.9% of the patients with Recovery filters had post-insertion DVT, while 11.8% had migration/tilt. SNF was excluded due to "small sample size and nonavailability of data". The authors noted that "the incidence of tilt/migration was the highest in the Bard RNF filter (11.8%) compared to each of the other filters ($p<0.004$) or to all other filters collectively ($p<0.0005$)." These results again highlight the high incidence of complications associated with the Recovery filter and that tilt/migration was significantly higher with this filter versus the Greenfield, TrapEase, and Tulip filters.

142. In 2012, Tam et al. published the results of a retrospective study of 363 patients who received Recovery filters at the Cleveland Clinic (Tam MD, Spain J, Lieber M et al. Fracture and distant migration of the Bard Recovery filter: a retrospective review of 363 implantations for potentially life-threatening complications. J Vasc Interv Radiol 2012; 23:199-205). Follow-up imaging was not systematic but revealed 26 limb fractures in 20 patients; 8 fragment migrations into pulmonary arteries; 7 into iliac/femoral veins; 1 into the right ventricle; and 1 into the renal vein. The authors concluded that the Recovery filter is associated with an estimated 5.5 year fracture risk of 40%.

143. This is an extraordinary adverse event risk for an implantable device.

144. In summary, a variety of studies in the medical literature demonstrated very high rates of adverse events with the Recovery filter. Complications were noted with the Asch study before the Recovery filter was released commercially and were confirmed by subsequent studies. Several of these studies were initiated by investigators who observed one or more complications with their patients and who then decided to do retrospective studies to see if this was a widespread problem.

ii) G2 Filter Studies

145. Because of the high complication rates associated with the Recovery filter, Bard released a redesigned filter called the G2. The Recovery filter was the predicate device for the G2. The G2 received FDA clearance through the same 510(k) process that led to the release of the Recovery filter. The G2 filter was intended to have fewer complications than the Recovery filter.

146. In 2008, Oliva et al. published a retrievability study of 120 Canadian patients with the G2 filter (Oliva VL, Perreault P, Giroux MF, et al. Recovery G2 inferior vena cava filter:

technical success and safety of retrieval. J Vasc Interv Radiol 2008; 19: 884-89). Only 51 of the 120 patients had filter removal. Among these 51, 12% had filter tilting (>15%); 18% had IVC penetration; and 3.9% had caudal migration. Although this retrievability study was not powered to examine safety and efficacy, an alarming number of complications were observed in this patient population. Despite the high complication rate, Bard never performed an adequately powered study to examine the safety and efficacy of the G2 filter.

147. Even this early study of the G2 filter showed an unacceptable and unreasonably high rate of complications.

148. In 2009, Binkert et al. published another retrieval study of the G2 filter (Binkert CA, Drooz AT, Caridi JG et al: Technical success and safety of retrieval of the G2 filter in a prospective, multicenter study. J Vasc Interv Radiol 2009; 20:1449-1453). This study is also known as the Everest trial. Among 100 patients who received the G2 filter, retrieval was attempted in 61 and was successful in 58. Among the 85 patients with complete data, 12% had caudal migration; 1.2% had filter fracture; 18% had filter tilt (>15%); and 26% had leg penetration.

149. This study demonstrated an extraordinarily high rate of complications with the G2 filter which was supposed to be an improvement over the Recovery filter. Importantly, the authors concluded that "caudal migration was observed as an unexpected phenomenon." Caudal migration had not been previously noted with the Recovery filter. This was a new phenomenon which occurred with the redesign of the Recovery filter. The Everest study is for G2 what the Asch study was for Recovery. The Everest study was a small retrievability study. There was limited follow up in the Everest study and there were already identifiable adverse events in this small patient population. The Everest study could have been continued with longer follow-up to examine safety, and thereby provided valuable information. Based on the early results and other information physicians would have expected Bard to do this. Even with the small sample size and limited follow up, high rates of migrations and other complications were evident. The Everest study identified an important safety problem for G2 that was not followed up by Bard.

150. Also in 2009, Charles et al. published a retrievability study of the G2 filter in 140 patients (Charles HW, Black M, Kovacs S, et al. G2 inferior vena cava filter: retrievability and safety. J Vasc Interv Radiol 2009; 20:1046-51). Only 26 patients had attempted filter retrieval. Tilting >15% was noted in 18.5% of patients with probable incorporation into the right lateral wall of the IVC in one.

151. It appears that this was a retrospective study although it is not identified as such in the paper. It does not appear that any systematic follow-up imaging was obtained in these patients so it is likely that true complication rates in this population were much higher than were reported in this paper.

152. Also in 2009, Lynch and Kekulawela published a retrospective analysis of 174 filter removals involving the G2. (Lynch, MD and Stephanie Kekulawela, MD, Removal of the G2 Filter: Differences between Implantation Times Greater and Less than 180 Days, J Vasc Interv Radiol 2009; 20:1200–1209). IVC penetration was found in 44%, fracture in 3.4%,

migration in 52% (12% had migration greater than 20 mm), and tilt more than 15 degrees in 13.8%.

153. In 2011, Zhu et al. published a retrospective study of 139 patients who received a G2 filter (Zhu X, Tam MD, Barthowlomew J, et al. Retrievability and device-related complications of the G2 filter: a retrospective study of 139 retrievals. J Vasc Interv Radiol 2011; 22:806-12). The authors found that G2 filter-related complications were common with limb penetration in 33; tilt >15% in 16; deformity in 10; IVC occlusion in 3; and fracture in 2.

154. Similar to previous publications, this study demonstrates a high rate of complications with the G2 filter.

155. Also in 2011, Damascelli et al. published an observational study involving 106 patients with 107 G2 filters placed, with follow-up at 3 and 6 months. (Damascelli, MD, et al., Use of a Retrievable Vena Cava Filter with Low Intensity Anticoagulation for Prevention of Pulmonary Embolism in Patients with Cancer: An Observational Study in 106 Cases, J Vasc Interv Radiol 2011; 22:1312–1319). The authors reported recurrent PE in 5.2% of patients, a removal rate of 13.2%, a rate of 0.9% for migrations, fractures, and penetrations (1 each), and filter tilt in 5.7%. The filter was removed in only 13.2% of patients.

156. In 2013, Mitsunaga and Yoon published a retrospective review of Kaiser patients who had filters implanted between 2000 and 2010, with follow-up through August, 2012. (Mitsunaga and Yoon, "Fracture Rate and Serious Complications of Vena Cava Filters," *Open Journal of Radiology*, Vol. 3 No. 2, 2013, pp. 85-90). Of 283 patients followed, 143 died. The authors reported no fractures in any of the filters studied (including the G2/G2x and Eclipse filters). One G2 filter perforated the aorta. This study is highly unusual in the extremely low rates of fracture reported compared with other studies. Only 3 cases of fracture were reported among 283 patients. This unusually low rate calls into question the adequacy of the imaging follow-up in these patients.

157. In 2014, An et al. published a study examining the prevalence of G2 filter fractures and fragment migration (An T, Moon E, Bullen J et al. Prevalence and clinical consequences of fracture and fragment migration of the Bard G2 filter: imaging and clinical follow-up in 684 implantations. J Vasc Interv Radiol 2014; 25:941-8). A total of 684 patients had follow-up imaging and were included in the study. A total of 16 fractured limbs were identified in 13 patients with 4 in the pulmonary arteries; 2 in the right ventricle; and 1 each in the pericardium, iliac vein and kidney. The estimated 5-year fracture prevalence was 38% (95% CI 22.9-54.8%). Despite the limited follow-up imaging that was performed in this retrospective study, the authors estimated that more than one-third of patients who receive a G2 filter will have fracture by 5 years.

158. A 33% chance of having a filter fracture by 5 years is an extraordinary rate of complications and would preclude the use of this filter.

159. The above studies examined the adverse event rates associated with the G2 filter – a filter that was developed to overcome the high adverse events rates associated with the Recovery

filter. As can be seen by the data presented, the G2 filter was also associated with unacceptably high rates of adverse events.

iii) Studies Comparing the Recovery and G2 Filters

160. Several studies compared the Recovery and G2 filters with respect to complication rates.

161. In 2008, Kim et al., published a retrospective analysis of 702 consecutive patients who received an IVC filter. (Kim, et al., A Comparison of Clinical Outcomes with Retrievable and Permanent Inferior Vena Cava Filters, J Vasc Interv Radiol 2008; 19:393-399). 40 Recovery and 7 G2 filters were placed. Of those, retrieval was attempted in 17 cases (14.5%) and successful in 100% for G2 and 42.9% for Recovery. The authors reported new symptomatic PE in 5% of Recovery patients and 6.5% of G2 patients, and new or worsening DVT in 17.5% and 14.3% respectively. The authors attributed the lack of symptomatic migration and penetration to the "infrequent occurrence of these events and the short duration of follow-up in our cohort."

162. In 2009, Cantwell et al. published a study comparing the Recovery filter in 128 patients with the G2 filter in 113 patients (Cantwell CP, Pennypacker J, Singh H et al. Comparison of the Recovery and G2 Filter as retrievable inferior vena cava filters. J Vasc Interv Radiol 2009; 20:1193-9). Only 55% of patients had retrieval attempted. Filter tilt was noted among 25% of Recovery patients and 11% of G2 patients. Filter fracture identified before attempted retrieval was 9% among Recovery patients and 0% among G2 patients. Importantly, just the attempts to retrieve the filters were associated with complications including cranial migration, caudal migration, filter fracture and filter embolization.

163. In 2010, Nicholson et al. published a study comparing fracture and embolization rates of the Recovery and G2 filters (Nicholson W, Nicholson J, Toerico P, et al. Prevalence of fracture and fragment embolization of Bard retrievable vena cava filters and clinical implications including cardiac perforation and tamponade. Arch Intern Med 2010 170:1827-31). A total of 80 patients underwent systematic follow-up fluoroscopy. Among the Recovery patients 25% had filter fracture compared with 12% of G2 patients. Among the Recovery patients with fracture, 71% had embolization to the right ventricle including 1 who had a hemorrhagic pericardial effusion requiring emergency surgery and another who had sudden death at home. The authors concluded that "The Bard Recovery and Bard G2 filters had high prevalence of fracture and embolization, with potentially life-threatening sequelae." They further observed that "If one were to extrapolate our observed prevalence of Bard G2 filter fractures to 50 months (essentially double the observed period), the prevalence of fracture would be identical to that observed for the Bard Recovery filter, thus challenging the hypothesis that the Bard G2 filter represents an improvement in fracture resistance." While authors published a later correction (the original number of reported patients was 83), the corrected numbers do not change the overall conclusions. (Letter to the Editor, "Correction to Article About Prevalence of Fracture and Fragment Embolization of Bard Retrievable Vena Cava Filters" Arch Intern Med 172(12) June 25, 2012, p. 972).

164. The Nicholson et al. study is one of the few studies that involved prospective systematic follow-up. In my opinion, their results show that both the Recovery and G2 filters have high rates of complications and that the G2 has complication rates similar to those of the Recovery filter. The study also demonstrates the value of medical monitoring with imaging studies of patients with these filters, and provides evidence of the number of patients with complications that are not identified until they are monitored.

165. In 2012, Vijay et al. published a study comparing the Recovery and G2 filters (Vijay K, Hughers JA, Burdette AS, et al. Fractured Bard Recovery, G2, and G2 express inferior vena cava filters: incidence, clinical consequences, and outcomes of removal attempts. J Vasc Interv Radiol 2012; 23:188-94). Among 548 patients presenting for filter retrieval, 63 had fractured filters (12%). The distal embolization rate of fractured filter components was 13%. They also found that filter fracture rates increase with longer dwell times.

166. Also in 2012, Dinglasan et al. published a retrospective study of 148 IVC filter removals between 2002 and 2010. (Dinglasan, MD, et al., Removal of Fractured Inferior Vena Cava Filters: Feasibility and Outcomes, J Vasc Interv Radiol 2012; 23:181–187). Of the 148 ICV filter removed, 15 were fractured. Of the 15 fractures, 6 (40%) were Recovery and 7 (47%) were G2. Of the patients with fractures, 33% complained of pain consistent with the location of the 19 fractured struts. 47% of the fractured struts migrated outside the IVC, including to the heart, pulmonary artery, and small bowel.

167. The above studies show that there are high rates of complications among patients with both the Recovery and G2 filters. Although the G2 filter was redesigned to overcome the excessive complication rates seen with the Recovery filter, reports in the medical literature indicate that there were still high rates with the G2 and that these rates were similar in magnitude to those seen with Recovery.

iv) Eclipse Filter Studies

168. There are comparatively fewer studies of Eclipse, likely due to the limited time it was on the market, and its similarities to the G2 filter. I did not find any studies documenting complication rates for Eclipse based on a retrospective review or randomized clinical trial.

v) Denali Filter Studies

169. The results of the DENALI clinical trial was published in 2016, involving 200 patients enrolled in a prospective, multicenter, nonrandomized study at 21 centers. (Stavropoulos et al. for the DENALI Trial Investigators, Analysis of the final DENALI trial data: a prospective mulicenter study of the Denali inferior vena cava filter, J Vasc Interv Radiol 2016; 27:1531-1538). Filter removal was attempted in 124 patients, and was successful in 121 (97.6%). According to the authors, there were no instances of filter fracture, migration, or tilt greater than 15 degrees at the time of filter retrieval or during follow-up. There were 5 instances of penetration (2.5%). The rate of recurrent, symptomatic PE was 3.0% and the rate of new or worsening DVT was 13.0%.

170. In 2016, Bos et al. published a retrospective analysis of the Denali and Celect (Cook) filters. (Bos, et al., Indwelling and Retrieval Complications of Denali and Celect Infrarenal Vena

Cava Filters, J Vasc Interv Radiol 2016; 27:1021–1026). Out of 116 patients who received follow-up scans, half were Denali filters and half were Celect. The authors reported a lower complication rate for Denali for all types of complications: Penetration-1 (1.7%) versus 12 (20.7%), tilt-1 (1.7%) versus 15 (25.9%), migration – 1 (1.7%) versus 2 (3.4%), and recurrent PE-2 (11.8% versus 5 (21.7%). There was one failed retrieval attempt out of 96, in a Denali filter (2.3%).

171. There is an extensive medical literature describing high complication rates associated with both the Recovery and the G2 filters. There is only limited literature available (at least yet) with respect to complication rates with the Eclipse and Denali filters.

vi) Conclusion

172. A number of the above studies follow the paradigm of signal detection (one or more adverse events associated with Bard devices), followed by further investigation (monitoring of patients and an assessment of the extent of the problem at a particular institution or institutions), followed by communication of the results to other physicians (through published studies). This is the type of investigation and communication that physicians expect a responsible device manufacturer to undertake.

I. BARD'S CRITICISMS OF THE MAUDE DATA WERE OVERSTATED AND DID NOT OBVIATE ITS DUTY TO COMMUNICATE THE RESULTS OF THESE ANALYSES TO PHYSICIANS

173. While Bard was aware of the high rates of adverse events associated with the Recovery G2, Eclipse, Meridian, and Denali filters, they attempted to downplay these rates among their own sales force. Bard's product brochure described "a marked improvement over currently available devices." (Recovery Brochure: BPV-17-01-00007760-763, and, "taking strength and stability to a new level." (G2 Brochure: BPV-17-01-00142912-915). Without disclosing the results of their analyses, Bard criticized the reliability of the

[redacted]

174. [redacted]

when trying to identify absolute rates of adverse events. MAUDE data is still of value in examining temporal trends with a particular device or for a comparison of similar devices marketed by different companies. The only time that underreporting could be an issue in these types of analyses is if there is selective or differential underreporting for different

devices. Under reporting generally, unless corrected for statistically, would underrepresent the true rate of complications with a device.

175. [redacted]

176. These findings go against the arguments advanced by Bard. Furthermore, the rate of events associated with the Recovery filter should be comparable to the predicate device since they were both made by the same company. Instead, the rate of events associated with the Recovery filter was much higher than those seen with the SNF (Betensky Report, 2017). Similarly, while the G2 and Eclipse filters were similar to the Recovery in terms of adverse event rates, G2 and Eclipse rates were also generally much higher than rates seen with the SNF (Betensky Report, 2017). This trend of high rates compared to SNF continued with respect to the available data (regarding fractures) with Meridian and Denali. (Betensky Report, 2017).

177. Third, Bard attempted to explain the high rates of adverse events seen with both the Recovery and G2 filters by claiming that most of these events were only identified at the time of filter retrieval. Since permanent filters are not retrieved, Bard suggested that there is a much lower likelihood that adverse events (e.g. tilt, fracture, perforation) will be identified with permanent filters that are never retrieved. Thus, Bard suggested that reported rates of adverse events are disproportionately identified with retrievable filters. In my opinion, Bard has not produced data to show that this is the case. To the contrary, studies suggest a relatively low retrieval rate, on the order of 3-13% cumulative, or 1.2-5.1% annual. (Gaspard, et al., *Retrievable Inferior Vena Cava Filters are Rarely Removed;* The American Surgeon, Vol. 75, No. 5, pp.426-428(3); May 2009; Sarosiek, et al., Association Between Inferior Vena Cava Filter Insertion in Trauma Patients and In-Hospital and Overall Mortality; JAMA Surg, Sept. 28, 2016; Parker, et al., Complication and Retrieval Rates of Inferior Vena Cava Filters, a Single-Center Retrospective Study; J of Vasc Surgery, Vol. 64, No. 3; Sept. 2016; Duszak et al., *Placement and Removal of Inferior Vena Cava Filters: National Trends in the Medicare Population;* J Am Coll Radiol, Vol. 8, Issue 7, pp 483-489; July 2011).

178. Finally, Bard references the reported failure rates of failures such as migration, fracture, and perforation in Table 2 of the Grassi article as "clinically accepted range described in professional society guidelines." Grassi CJ: JVIC. 2003; 14:S271-S275, BPVE-01-01455684-687 at 685. My criticism of Bards' use of this paper are discussed below.

J. BARD'S INAPPROPRIATE COMPARISON OF ADVERSE EVENT RATES WITH GRASSI ARTICLE TO JUSTIFY HIGH EVENT RATES WITH RECOVERY

179. [redacted]

180. [redacted]

181. A major argument that Bard used in attempt to counter the growing shift away from Bard retrievable filters was to say that the event rates observed with Recovery G2, Eclipse, Meridian, and Denali fell within the so-called "threshold" or "acceptable range" values established in the 2003 Grassi article (Grassi CJ, Swan TL, Cardella JF, et al for the Society of Interventional Radiology Standards of Practice Committee. Quality Improvement Guidelines for Percutaneous Permanent Inferior Vena Cava Filter Placement for the Prevention of Pulmonary Embolism. J Vasc Interv Radiol 2003; 14:S271-S275).

182. [redacted]

183. [redacted]

184. [redacted]

185. Importantly, there were major methodological issues with the Grassi article which made it inappropriate to use for comparison purposes. These methodological issues made Bard's use of the article for comparison "thresholds" misleading for both their sales force and for clinicians. Bard's comparison of their spontaneous reports versus sales complication rates to the Grassi rates was inappropriate and misleading, and grossly misrepresented and overrepresented the rate of spontaneous reports of complications that were expected and acceptable for Bard's filters.

186. [redacted]

187. Second, the Grassi article was not a true guidelines statement similar to the types of statements that are issued by the ACC/AHA or other national and international societies. For example, there were no recommendations issued in the article and there were no levels of evidence provided. There was no methodology described in the paper. The article was more of a consensus statement about quality assurance for hospitals, and does not even purport to be a consensus regarding an acceptable range of complication rates. Guidelines are based on the best evidence available and typically reference data from randomized controlled trials. The title of the Grassi article is misleading. It is not a guidelines statement with recommendations and levels of evidence. It does not pool data from the cited studies to give robust point estimates with confidence intervals. It is not an adequate basis to establish thresholds for safety and does not purport to be.

188. Third, it was not the intent of the authors that the article be used to establish acceptable thresholds for safety. The article did not take into account different types of patient populations, and it involved old studies none of which involved retrievable filters.

189. There are no thresholds in Table 2, they are only in Table 1 (which deals primarily with failures more closely associated with operator input or potential error than inherent product defect issues). Table 2 does not contain any thresholds, and are only reported as "other trackable events". These rates do not reflect any sort of consensus of opinion among interventional radiologists as to what should be expected or accepted, they are simply a report of medical literature concerning these failure modes that were available at the time of the 2003 article. A review of the sources of those reported failures demonstrates its limitations. For example, the entire basis of the SIR fracture failure rate is based upon two studies by a team of University of Arkansas doctors, (Complications of the Nitinol Vena Caval Filter, JVIR 1992; 3:401-408), in 1992 and 1993. The 1992 paper studied 20 patients and found two fractures, which provides the 10% failure rate reported in the article. The same team expanded the study to 320 patients for the 1993 article and found a 2% fracture rate, which provides the 2% failure rate contained in Table 2. The two studies were limited to one hospital that used filters from between 1985-1992, which means that none of the

studies reported on retrievable filters, nor to design changes on older devices, or the elimination of certain devices no longer being marketed and used between 1992 and 2003. Nor the emergence of newer designed devices. None of the updates to the SIR paper has reviewed or added any new medical literature to the fracture rates reported in Table 2 – until 2017 (see ACR-SIR-SPR Practice Parameter referenced, below). In summary, the entirety of what Bard calls the SIR "guideline" upper limit of 10% for fracture is based on a single study of 20 patients using permanent filters that ended in 1992. In my opinion it is misleading and erroneous to suggest to doctors or the public that this rate represents a reasoned consensus among interventional radiologists, or that it has any application to acceptable failure rates for retrievable filters.

190. The authors state in their article that the numbers were intended "To be used in quality improvement programs." According to Dr. Grassi's deposition, the article should not be used and was not intended to be used to indicate safety thresholds (Grassi Depo Aug 22 2013, 59:2-19). As Grassi et al. stated in their article, the data presented should only have been used to identify several types of complications associated with IVC filters that should be tracked. The numbers quoted in the article were not intended as thresholds for safety but rather as indicators for when quality assurance mechanisms should be initiated at hospitals. Moreover, many of the references recommend that steps be taken to design safer and more effective devices. Indeed, the latest revision of the Grassi paper, (ACR–SIR–SPR Practice Parameter for the Performance of Inferior Vena Cava (IVC) Filter Placement For The Prevention Of Pulmonary Embolism (Revised 2016 (Resolution 18), available at https://www.acr.org/~/media/ a569be8f18ae4cfaa2868b6c0984dbd8.pdf, last visited 1/27/17), indicates that the reported rate for penetration is 0-100%, for migration, 0-25%, and for fracture, 0-50%. It makes no sense for these to represent standards for failure, and a comment below Table 2 confirms this: "The data in the table represents reported outcomes from various publications and not the SIR standard for complications."

191. Fourth, this article does not break down the numbers by filter type. The ranges given are often very wide (e.g. migration 0-18% and fracture 2-10% and IVC penetration 0-41%). Because there can be wide ranges between different filters, the thresholds given are not of practical use. For example, the suggested threshold of <1% for death is inadequate if one type of filter has a death rate of 0.9% and another has a death rate of 0.1% - a 9-fold difference.

192. [redacted]

[redacted]

K. RESPONSIBILITY OF BARD TO DO LARGE SAFETY AND EFFICACY STUDIES

193. [redacted]

194. Bard assured its consultant Dr. Murray Asch that it would conduct a traditional long-term clinical trial on safety and effectiveness before launching the Recovery filter into the open commercial market which bard failed to do. [redacted]

195. [redacted]

[redacted]

196. Bard's position seems to be that Recovery was substantially equivalent to its predicate device the SNF, so clinical trials were not required before it could be marketed. They only needed the Asch study to document retrievability, because the SNF was not retrievable. According to DeCant, clinical trials should not have been done because issues regarding distensibility of the IVC should be done in animals and humans should not be used as "guinea pigs" for these kinds of studies 63:16-64:11; 379:18-381:13).

197. [redacted] it is my opinion that Bard had the responsibility to do adequately powered safety studies once a safety signal had been detected. Bard had the responsibility to do a large randomized controlled trial that was adequately powered to look at safety and efficacy. It would be a misrepresentation and improper disregard for the safety of patients for Bard to not provide safety data that indicated high rates of complications with its products. I have a responsibility to my patients to provide them the best devices available. Without access to all the safety data available, I may be giving my patients an inferior and dangerous product.

198. Bard had the opportunity, ample justification and responsibility based on reasonable physician and patient expectations to do large safety and efficacy studies in order to address the safety signals they identified. It is important to note that the smaller retrospective studies discussed above are useful for detecting safety signals or problems with a device. In particular, the totality of these studies allow physicians to draw the conclusion that the safety profile of the devices is unacceptable, particularly when viewed in combination with other data (such as adverse event reports, bench testing, etc.). In the absence of RCTs, this is information that physicians would expect a responsible device manufacturer would evaluate and communicate to them. These studies are not, however, designed or sufficient to serve as safety studies to prove that the devices are safe and efficacious (as discussed above, in reference to the Asch study, and below, with reference to study power). Put another way, one can draw the conclusion from such studies that the complication rate is unacceptable, but not that the device is sufficiently safe or efficacious.

199. In the medical literature, there has never been a large randomized controlled trial of Recovery versus SNF or G2 versus SNF. Most studies of these devices in the medical literature are registry studies that followed a group of patients with filters and then reported the complication rates. Even among these studies, the majority are retrospective and not prospective studies. These types of studies, while they can and should be used to detect if complications are occurring and the extent of complications in discreet populations, these studies are unable to provide statistical testing to prove equivalence because they do not include control or comparison groups.

200. Bard could have easily pooled data from different registry studies into a meta-analysis. Pooled data from SNF, Recovery, G2/G2X, Eclipse and Meridian registries could have easily been done. These types of analyses are not as robust as that from randomized

controlled trials, but meta-analyses are highly feasible and are relatively easy to perform at low cost and in a short space of time.

201. Nevertheless, despite the absence of any large randomized controlled trials as well as the absence of any meta-analyses, the totality of the data from the medical literature clearly supports the Bard internal analyses of the adverse event/sales data, confirmed by the Betensky analyses, and complemented by the internal Bard migration resistance data, provides compelling and reliable evidence of significantly higher complication rates with the Recovery, G2/G2X, Eclipse and Meridian, versus the SNF.

202. The ideal study that should have been performed by Bard to evaluate the safety and efficacy of the Recovery G2/G2X, Eclipse and Meridian, filters after problems came to light would have been a randomized controlled trial. Randomized controlled trials are considered the "gold standard" evidence in medicine. If, for example, a company wanted to prove that the Recovery is substantially equivalent to the predicate device which was the SNF, the best evidence would be an adequately powered trial randomizing patients to Recovery versus SNF and then follow the patients forward with systematic imaging and long term clinical follow up to see what the outcomes are. If the trial has an adequate sample size and therefore power, it can identify whether the Recovery and SNF are substantially equivalent.

203. It is a straightforward exercise to identify the sample size required for a study to identify whether a device is associated with a complication rate below a certain number. Based on my calculations, this type of trial would require as few as hundreds and at most a few thousand patients in order to be adequately powered. This type of trial would have to be multicenter in design and have follow-up longer than 6 months. It would also need to include systematic follow-up imaging studies.

204. In fact, a study such as the one described above is currently underway. The PRESERVE Trial (Appendix D) is comparing the safety and efficacy of several types of retrievable IVC filters. This is a multicenter study at 60 sites involving 1800 patients with 24 month follow-up. The PRESERVE Trial is the type of study that Bard should have commissioned to show that the Recovery and G2 filters were safe and effective and substantially equivalent to their predicate devices (SNF for Recovery and Recovery and SNF for G2).

205. Following the Asch retrievability study, if Bard wanted to properly follow up on safety signals, Bard could and should have done adequately powered studies to look at the safety and efficacy of the Recovery filter. It would have been optimal to do head to head trials with the Recovery versus other retrievable devices to look at long-term safety and efficacy. These trials would have required systematic monitoring and surveillance and routine long term imaging of patients to objectively and prospectively identify complication rates and to see whether one filter type is better or safer than another.

206. Because there were known complications associated with Bard's IVC filters (including 1 patient with migration in Asch's original series of just 32 patients, a 33rd patient with fractures, and another with tilt, and multiple cases of caudal migration with the G2 filter in the Everest study), the onus was on Bard to do the large safety and efficacy studies required before allowing physicians to implant these devices in large numbers of patients. Follow-

up for these patients would have had to be on the order of at least a year or more since many of the retrievable filters were not removed but, in fact, were left in place permanently. Long term surveillance and monitoring in the context of a clinical trial would have confirmed with the highest level of evidence that there is a significant complication rate with these filters. Such studies would be feasible and relatively quick to do.

207. As a clinician and a clinical epidemiologist, it is my opinion that the clinical decision to recommend that a patient use a new device should be evidence-based for efficacy and safety. I do not see that evidence for the Recovery and G2 filters. It is misleading to make claims about safety and efficacy without evidence. Evidence available from studies that have addressed the subject, such as those by Tam (Recovery) and An (G2) reported more complications the longer the filters are left in place. The increased risk with longer durations of implantation justifies medical monitoring with imaging studies of this population of patients. In addition, Bard should have done large prospective (not retrospective) registries/cohort studies, head to head trials, and administrative database studies to examine the safety of the Recovery and G2 filters. As a clinician and a clinical epidemiologist, in order to establish evidence of safety and efficacy, this is what is needed. The safety signals need to be followed up. Making filters retrievable led to design modifications which led to less robust devices and which subsequent complications such as tilt, migration, and fracture.

208. No adequate study on the safety and efficacy of Recovery and G2 was ever performed. In the absence of such studies, the importance of other forms of evidence, including prospective and retrospective studies, case series, and adverse event reports should not be downplayed.

209. A single case or a small number of unusual cases can be enough to be construed as a safety signal. For example, Bard's paid consultant/expert Dr. Feigel issued a public health alert on behalf of the FDA as the Director for the Center for Devices and Radiological Health based on two reports of death associated with the use of deep brain stimulators. (Feigel Dep., pp. 85-87). A Key Opinion Leader for Bard, Dr. Gary Cohen, similarly stopped using Bard filters after he learned about Recovery migrations. (Cohen Deposition, 1/26/17, p. 71:12-23).

210. There were alternate filter designs that were safer than the Recovery and G2 filters. Complication rates with the SNF were lower, and thus, the Recovery and G2 filter designs themselves were inferior to the design of the predicate device.

L. DESIGN CONSIDERATIONS FOR LARGE SAFETY AND EFFICACY STUDIES FOR RETRIEVABLE FILTERS

211. I performed several sets of calculations of power, sample size, and confidence intervals (Appendices E-G). The first set of calculations examined confidence interval sizes depending on various sample sizes (Appendix E). These calculations do not refer to any specific study. I chose different sample sizes and different potential complication rates and used these numbers to calculate the size of confidence intervals around the point estimates of the complication rates. The second set of calculations are sample size and power

calculations if one wanted to design a clinical trial comparing a predicate device with low complication rates to a newer device with higher complication rates (Appendix F). These calculations were used to calculate sample sizes for the two arms of a trial that would have adequate power to identify various differences in complication rates between devices. The third set of calculations were to determine sample size calculations for clinical trials – again to have adequate power to examine differences in complication rates between devices – this time I used complication rates from the Grassi article (Grassi CJ: JVIC. 2003; 14:S271-S275; Appendix G).

212. The results of these analyses demonstrate that to be able to identify a 5% absolute difference in rates between a new device and a predicate device with an alpha of 0.05 and a power of 0.80, a clinical trial would require over 1000 subjects (e.g. 10% to 15%; 20% to 25%; 30% to 35%). If one wanted to identify even smaller differences (e.g. 3-4% absolute difference in rates between devices), even larger sample sizes would be required. Thus, the small studies that were commissioned by Bard to show retrievability of the Recovery (Asch study) and the G2 (Everest study) were completely inadequate to show substantial equivalence to predicate devices or to examine safety and efficacy.

213. It would have been ethical to perform a randomized controlled trial of Recovery and SNF. Both devices were first available for commercial use as permanent filters. This was also true for G2. It was only later after their release that Recovery and G2 received their indications for retrievability. Certainly, it would have been ethical to randomize patients who need permanent filters to SNF versus the other filters, since they all had an indication for permanent implantation (prior to when Bard had evidence of safety concerns).

M. MINIMAL EVIDENCE OF THE VALUE OF RETRIEVABLE IVC FILTERS

214. There are almost no studies in the medical literature exploring the impact of IVC filters on mortality. The PREPIC study, one of the best-designed and highly cited studies done in this area, suggests that IVC filters have no impact on survival (Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena cava filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. N Engl J Med 1998; 338:409-15). These investigators concluded that: "In high-risk patients with proximal deep-vein thrombosis, the initial beneficial effect of vena caval filters for the prevention of pulmonary embolism was counterbalanced by an excess of recurrent deep-vein thrombosis, without any difference in mortality. Our data also confirmed that low-molecular-weight heparin was as effective and safe as unfractionated heparin for the prevention of pulmonary embolism."

215. The 8-year follow-up from the PREPIC study showed the same results (The PREPIC Study Group. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (prevention du risqué d'embolie pulmonaire par interruption cave) randomized study. Circulation 2005; 112:416-22). The authors found that "At 8 years, vena cava filters reduced the risk of pulmonary embolism but increased that of deep-vein thrombosis and had no effect on survival."

216. Anticoagulation has been shown to decrease mortality in patients with DVT and PE (PREPIC 2). However, the question remains open whether IVC filters decrease mortality in patients who cannot receive anticoagulation or if IVC filters decrease mortality among patients who have recurrent PE on anticoagulation.

217. A systematic review/technology assessment by Walsh from UCSF indicates that, after a systematic search of the medical literature, their group could find only two trials of filters versus anticoagulation (Walsh J. Safety and effectiveness of inferior vena cava filters used to protect against pulmonary embolus. California Technology Assessment Forum. Feb 16, 2011. San Francisco, CA). The Walsh systematic review/technology assessment suggests that filters may decrease the rate of recurrent pulmonary emboli, but that filters also increase rates of DVT and inferior vena cava thrombosis while there is no reduction in mortality. Thus, the authors suggest that randomized controlled trials of routine filter placement vs anticoagulation plus no filter placement are needed.

218. Bard witnesses, including Mr. DeCant, have testified that the benefits of IVC filters outweigh their risks and complication (Decant deposition, 440:15-441:5; DeFord deposition, 118:12-119:14; Ganser deposition, 323:23-324:9). According to the Walsh report, there is no evidence of decreased mortality with the use of IVC filters. At the same time, IVC filters are associated with an increase in DVTs and vena cava thrombosis. Many patients implanted with retrievable filters end up receiving anticoagulation. The idea advanced by Bard that IVC filters save lives and thus it was not ethical or feasible to do adequately controlled and properly powered studies showing safety and efficacy is untenable. It was clearly feasible to do this type of study in patients receiving filters for prophylaxis.

219. Prophylaxis with IVC filters may be of no clinical benefit and may actually be harmful. (Bikdeli, et al., Data Desert for Inferior Vena Caval Filters: Limited Evidence, Supervision, and Research, JAMA Cardiology, 1/1/2017, 2:3-4. Trauma/bariatric surgery patients can often receive low dose anticoagulation, so it is not at all clear that there is an indication for a retrievable IVC filter in these patients. In addition, the de novo rates of pulmonary embolism in these types of patients are low (PREPIC 2) while IVC filters have complications associated with them. Thus, the risk benefit of using retrievable IVC filters for prophylaxis has not been well demonstrated. Consequently, IVC filters should not be used in these circumstances except under strict circumstances – for example, a patient with a documented pulmonary embolus who has an absolute contraindication to anticoagulation. (American Society of Hematology, Choosing Wisely: Then Things Physicians & Patients Should Question, 2015, p. 15-18). To my knowledge, there is little evidence based medical support for routine prophylaxis with retrievable IVC filters.

220. One of the few studies to examine the utility of IVC filter prophylaxis was done by Brunson et al. (Brunson A, Ho G, White R, Wun T. Inferior vena cava filters in patients with cancer and venous thromboembolism (VTE): patterns of use and outcomes. Thromb Res. 2016; 40 Suppl 1:S132-41). This study showed that there is high variability among centers with respect to the prophylactic use of IVC filters in patients with DVT or PE. It appears that most of the treated patients could have been treated with anticoagulation instead. The study suggested that there was no clinical benefit to the prophylactic use of IVC filters in this

population and that their use was actually associated with an increase in complications – specifically DVT and bleeding. (See, also, Hemmila, et al., Prophylactic Inferior Vena Cava Filter Placement Does Not Result in a Survival Benefit for Trauma Patients, 262:4 Annals of Surgery, 577, 2015). The Hemmila study concluded that "High rates of prophylactic IVC filter placement have no effect on reducing trauma patient mortality and are associated with an increase in DVT events."

221. I hold all of my opinions to a reasonable degree of medical certainty. I reserve the right to supplement this report if I receive additional pertinent information.

Dated: February 10, 2017

Mark J. Eisenberg, MD MPH FACC FAHA

V. APPENDICES

Appendix A. CV

Appendix B. Prior Testimony 2012-2017

8/7/16 *Austin v. Bard*, Montreal, Canada

Appendix C. Reporting Rate Calculations

Filter	Event	Time-period	Event Count	Sales Count	Rate	Exceeds threshold ?	STD-002 Severity	Threshold requiring correction	Event Count Source	Sales Count Source
[redacted]										

Filter	Event	Time-period	Event Count	Sales Count	Rate	Exceeds threshold ?	STD-002 Severity	Threshold requiring correction	Event Count Source	Sales Count Source
[redacted]										

Filter	Event	Time-period	Event Count	Sales Count	Rate	Exceeds threshold ?	STD-002 Severity	Threshold requiring correction	Event Count Source	Sales Count Source
[redacted]										

Filter	Event	Time-period	Event Count	Sales Count	Rate	Exceeds threshold ?	STD-002 Severity	Threshold requiring correction	Event Count Source	Sales Count Source
[redacted]										

Appendix D. The PRESERVE Trial

Predicting the Safety and Effectiveness of Inferior Vena Cava Filters (PRESERVE)

This study is currently recruiting participants. (see Contacts and Locations) Verified October 2015 by New England Research Institutes

Sponsor:

New England Research Institutes

Collaborators:

IVC Filter Study Group Foundation (IDE Sponsor)

ALN Implants Chirurgicaux

B. Braun Interventional Systems, Inc

Bard Peripheral Vascular, Inc.

Cook

Cordis Corporation

Rex Medical

Information provided by (Responsible Party):

New England Research Institutes

Tracking Information First Received Date ICMJE March 2, 2015 Last Updated Date September 27, 2016 Start Date ICMJE October 2015 Estimated Primary Completion Date May 2018 (final data collection date for primary outcome measure) Current Primary Outcome Measures ICMJE (submitted: March 2, 2015)

- Composite safety endpoint of freedom from clinically significant perforation after successful filter placement, filter embolization, caval thrombotic occlusion, deep vein thrombosis, and perioperative serious adverse event [Time Frame: within first 365 days (± 30 days)] [Designated as safety issue: Yes]

  Clinically significant perforation is defined as protrusion of filter legs through the wall of the IVC causing hemorrhage or hematoma or touching, impressing, or perforating another organ or that triggers the decision to remove the filter; resulting in an attempt to remove the IVC filter or requiring other intervention. Filter embolization is defined as movement of the filter or its components to a distant anatomic site completely out of the target zone after successful filter placement, confirmed by imaging. Caval thrombotic occlusion is defined as presence of an occluding thrombus in the IVC after filter insertion and documented by ultrasound (US), computed tomography (CT), magnetic resonance (MR) imaging, venography, or autopsy; this may be symptomatic or asymptomatic after successful filter placement. Deep vein thrombosis (DVT) is defined as new symptomatic DVT post-deployment, as determined by standard of care imaging. Serious adverse event is defined by ISO 14155.

- Composite effectiveness endpoint of procedural and technical success without occurrence of clinically significant pulmonary embolism [Time Frame: at 12-months in-situ or 1-month post-retrieval (whichever comes first)] [Designated as safety issue: No]

Original Primary Outcome Measures ICMJE Same as current Change History Complete list of historical versions of study NCT02381509 on ClinicalTrials.gov Archive Site Current Secondary Outcome Measures ICMJE Not Provided Original Secondary Outcome Measures ICMJE Not Provided Current Other Outcome Measures ICMJE Not Provided Original Other Outcome Measures ICMJE Not Provided Descriptive Information Brief Title ICMJE Predicting the Safety and Effectiveness of Inferior Vena Cava Filters Official Title ICMJE Predicting the Safety and Effectiveness of Inferior Vena Cava Filters Brief Summary PRESERVE is a multi-center, prospective, open-label, non-randomized investigation of commercially available IVC filters from 6 manufacturers placed in subjects for the prevention of pulmonary embolism (PE). This study will enroll approximately 1,800 IVC filter subjects at up to 60 sites in the US. All treated subjects will be evaluated at procedure, 3-months, 6-months (phone), 12-months, 18-months (phone), and 24-months post-procedure. The primary objective of this investigational device exemption (IDE) clinical investigation is to evaluate the safety and effectiveness of the commercially available IVC filters (retrievable and permanent) in subjects with clinical need for mechanical prophylaxis of PE with an IVC filter. Detailed Description Not Provided Study Type ICMJE Observational Study Design ICMJE Observational Model: Cohort Time Perspective: Prospective Target Follow-Up Duration Not Provided Biospecimen Not Provided Sampling Method Non-Probability Sample Study Population Subjects requiring the placement of one of 6 IVC filters for the prevention of PE. Condition ICMJE Pulmonary Embolism Intervention ICMJE Device: IVC Filter Study Group/Cohort (s) IVC Filter

IVC filter for the prevention of PE

Intervention: Device: IVC Filter Publications * Not Provided * Includes publications given by the data provider as well as publications identified by ClinicalTrials.gov Identifier (NCT Number) in Medline. Recruitment Information Recruitment Status ICMJE Recruiting Estimated Enrollment ICMJE 1800 Estimated Completion Date May 2019 Estimated Primary Completion Date May 2018 (final data collection date for primary outcome measure) Eligibility Criteria ICMJE

Inclusion Criteria:

- Male or Female, age 18 years or older;
- Requires IVC filter for prevention of pulmonary embolism (PE);
- Provide written informed consent and written HIPAA authorization prior to initiation of study procedures;
- Willing to comply with the specified follow-up

Exclusion Criteria:

- Subject is unable to participate in study evaluations pre- and post-treatment
- Known sensitivity to contrast or serious contrast reaction such as anaphylaxis for which premedication is known to be unsuccessful in alleviating symptoms

Gender Both Ages 18 Years and older (Adult, Senior) Accepts Healthy Volunteers No Contacts ICMJE

Contact: Jessica Lamp, BA 617-972-3140 jlamp@neriscience.com

Contact: Sandi Siami, MPH ssiami@neriscience.com

Listed Location Countries ICMJE United States Removed Location Countries Administrative Information NCT Number ICMJE NCT02381509 Other Study ID Numbers ICMJE M01482 Has Data Monitoring Committee Yes Plan to Share Data Not Provided IPD Description Not Provided Responsible Party New England Research Institutes Study Sponsor ICMJE New England Research Institutes Collaborators ICMJE

- IVC Filter Study Group Foundation (IDE Sponsor)
- ALN Implants Chirurgicaux
- B. Braun Interventional Systems, Inc
- Bard Peripheral Vascular, Inc.
- Cook
- Cordis Corporation
- Rex Medical

Investigators ICMJE

Study Chair: David L. Gillespie, MD, RVT, FACS Southcoast Health System

Study Chair: Matt Johnson, MD Indiana University School of Medicine

Information Provided By New England Research Institutes Verification Date October 2015 ICMJE Data element required by the International Committee of Medical Journal Editors and the World Health Organization ICTRP

Appendix E. Confidence Interval Calculations

Calculated using M/L McCallum Layton CI Calculator for Proportions

Sample Size	Complication Rate (%)	95% Confidence Interval (±)
30	1	3.56
	5	7.80
	10	10.74
	15	12.78
	25	15.49
50	1	2.76
	5	6.04
	10	8.32
	15	9.90
	25	12.00
100	1	1.95
	5	4.27
	10	5.88
	15	7.00
	25	8.49
1000	25	2.68

Appendix F. Sample Size and Power Calculations

Assumes alpha of 0.05 and a power of 80%. Higher power would require even more subjects.

Complication Rates		
Predicate Device (%)	New Device (%)	Sample Size Needed (per arm)
0	5	152
0	10	73
0	15	47
10	15	686
10	20	199
10	25	100
20	25	1094
20	30	293
20	35	138
30	35	1377
30	40	356
30	45	162

Appendix G. Sample Size Calculations (if one were designing a study to see if a retrievable filter has a significantly higher complication rate than thresholds in the Grassi article).

Calculations assume an alpha of 0.05 and a power of 80%. Output is sample size per arm if one wanted to design a prospective study to see if Recovery complication rates were 10% higher than Grassi thresholds or if they doubled "trackable event rates."

	Threshold (Grassi %)	Able to Identify (%)	Number per arm
Death	<1	10	100
Recurrent pulm emboli	5	15	140
IVC Occlusion	10	20	199
Filter Embolization	2	10	137
Access Site Thrombosis	1	10	100
IVC Penetration (0-41)	20	30	293
Migration (0-18)	9	18	225
Filter Fracture (2-10)	6	12	356